

Message

From: Schlosser, Paul [Schlosser.Paul@epa.gov]
Sent: 10/1/2018 3:16:49 PM
To: Mel Andersen [Ex. 6 Personal Privacy (PP)]
CC: Thayer, Kris [thayer.kris@epa.gov]; Bahadori, Tina [Bahadori.Tina@epa.gov]; Schlosser, Paul [Schlosser.Paul@epa.gov]
Subject: RE: meeting to outline advances in Mn-PBPK modeling
Attachments: 2018 09 18 Umbrella PBPK QAPP.PDF

Hi Mel,
Cc: Kris Thayer, Tina Bahadori

Sorry it's taken a bit to get back to you. It would be good to have a meeting where I and other EPA staff can hear about your revisions of the model and have some discussion of that. Because this is something that could potentially be used in an NCEA/IRIS analysis, other EPA staff should attend (including Will Boyes, Elaina Kenyon, Annie Jarabek, and Kris Thayer), which makes scheduling a bit more difficult. We'd like to plan something for mid-November. I think that Monday-Thursday the week of Nov. 12 should work, or possibly the 19th or 20th (Monday/Tuesday of Thanksgiving week). Can you check, come back with a few specific dates and time windows in there when you and others on the modeler team would be available?

Also, you should know that all materials presented, a roster of the meeting attendees, and a summary of action items (if applicable) will be posted on the IRIS website under "stakeholder requested meetings."

<https://cfpub.epa.gov/ncea/iris2/events.cfm#stakeholderMeetings>

Second, as you may know from Harvey and the project he's leading on chloroprene, we now have a quality assurance process plan (QAPP) that we follow in evaluating any PBPK or other type of model we might consider for use. This is an implementation of newer policies set by EPA's Office of Research and Development (ORD) regarding computational models. It also reflects experience from evaluating quite a few PBPK models for use in risk assessments and many discussions among EPA's Pharmacokinetics Workgroup (PKWG), and others. You may recall this paper on which Eva McLanahan was lead author, which was part of our evolution in this direction:

<https://www.ncbi.nlm.nih.gov/pubmed/22045031>. A copy of the QAPP is attached.

So, the new ORD policy and the PKWG QAPP raise the bar on what is required for model use for NCEA assessments. While I know that the Mn models were developed under the oversight of EPA staff with good expertise (Will, Elaina, and Annie), that was specifically for the proposed use of MMT as a fuel additive, which was expected to result in highly soluble Mn particulate forms. To use a model in an NCEA assessment today, it will need to pass our current, more rigorous standards (QAPP) where the potential application to multiple Mn forms will likely need to be considered.

As part of our meeting, I can present an over-view of the QAPP, its primary features and requirements, with some examples of errors or issues we find and how they might be addressed. It's not just a matter of having reproducible model code and traceable parameters, but biological realism balanced by parsimony in model structure/parameters. Our hope is that over time those who are developing new models (or revising old ones) for possible use in risk assessments will be aware of and follow these standards, as it would then make our job of reviewing a model and determining applicability easier. We'd much rather review a model that is 'clean' than be trying to triage.

Frankly, I think we could have a more substantive meeting, make better use of the time if we could first get copies of the revised model workspaces and at least a draft report describing what changes were made, showing model fits to data, and any other results you plan to present. If we could get these in October, that would allow us to do an initial, if cursory review, and possibly flag some things for discussion. Preferably the workspace would have the scripts that produce the plots and tables, as checking those is part of the QA process.

Sincerely,
-Paul

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**From:** Mel Andersen [mailto:[Ex. 6 Personal Privacy \(PP\)](#)]  
**Sent:** Monday, September 24, 2018 11:43 AM  
**To:** Schlosser, Paul <[Schlosser.Paul@epa.gov](mailto:Schlosser.Paul@epa.gov)>  
**Subject:** meeting to outline advances in Mn-PBPK modeling

Paul,

The team developing PBPK models for manganese would very much appreciate the opportunity to schedule a meeting with you in October. The specifics about our request for a meeting and possible dates are included in the attached letter. Let me know if you have any questions and whether one of the proposed days works with your schedule.

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